e.g., FDA (2015b). As a result, this can lead to a physicochemical window of consistency for the same RP that may vary somewhat from one regulatory region to another due to slight variations in manufacturing at different sites of production and/or to the significant differences in the number of commercially available RP lots available for analysis, coupled with the resulting inherent nature of statistical variations, especially when the total RP lot population is low for one or more of these different specific regulatory regions.

2.6 ANALYTICAL PHYSICOCHEMICAL CHARACTERIZATION CAPABILITIES IN ASSESSING BIOPHARMACEUTICAL CONSISTENCY AND BIOSIMILARITY

An important point to realize when making copies of biopharmaceuticals that have or will be coming off patent protection in the next few years is that these biopharmaceuticals were developed and approved using analytical technologies that existed two to three decades ago. Since that time, an explosion of improvements in analytical instrumentation and techniques, especially in the areas of biochemical and biophysical analysis, has occurred that has greatly enhanced our ability to characterize complex biomacromolecules such as biopharmaceuticals (Berkowitz et al., 2012; Marino et al., 2015). One area that has facilitated many of these achievements has been associated with developments in digital electronics and computers (in terms of both hardware and software). In addition, advances in other scientific and technical areas (e.g., material science, higher sensitivity detectors), as well as advances in many unrelated scientific areas, coupled with the continuing ingenuity of scientists and engineers, have contributed greatly to the development of new and improved technologies and analytical instruments with ever greater analytical power. With this greater analytical capability we are now able to analyze the earlier approved commercial biopharmaceuticals in much greater detail with much greater resolution, sensitivity, precision, and accuracy (frequently in much less time and using much less material) relative to when they were first approved. As a result, when an RP is characterized by a biosimilar manufacturer today, more detailed information will likely be uncovered about that RP than what was known when it was initially approved. It must also be realized that these earlier approved biopharmaceuticals are more likely to display less consistent manufacturing in comparison to today's biopharmaceuticals (which includes biosimilars) owing to the more recent advances and improvements in today's manufacturing resulting from implementing process analytical technology (PAT) (FDA, 2004; Glassey et al., 2011; Kozlowski and Swann, 2006; Rathore et al., 2010) and quality by design (QbD) concepts (FDA, 2009b; ICH, 2005; Kozlowski and Swann, 2006; Rathore and Mhatre, 2009).

Nevertheless, even with the significant advances and improvements in our present manufacturing and analytical instrumentation, our present limited knowledge, capability, and know-how as to what exactly needs to be altered to produce a biosimilar so that it adequately displays the specific physicochemical characteristics that will make it highly similar to the RP to receive regulatory approval, is just as big a problem and challenge as the analytical assessment part. Analytics can establish